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Biopharmaceutics and metabolism of yohimbine in humans

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Abstract

The biopharmaceutics of yohimbine (YO) and the pharmacokinetics of 10-hydroxy-yohimbine (10-OH-YO) and 11-hydroxy-yohimbine (11-OH-YO) were investigated in healthy subjects following i.v. (5 mg) and oral (8 mg) dosing. One subject was found as a slow hydroxylator of YO. The mean (±S.D.) oral absolute bioavailability of YO was 22.3±21.5%. Total plasma clearance (CL) and renal clearance (CL_r) of YO following i.v. dosing were 0.728±0.256 ml/min and 0.001±0.002 ml/min, respectively. Based on the steady-state volume of distribution (V_{ss}), YO had a relatively low distribution (V_{ss}=32.2±12.1 l). The overall renal excretion of YO, 10-OH-YO and 11-OH-YO, expressed as percent of the dose of YO administered, were not different following i.v. and oral dosing, and were around 0.1, 0.2 and 14%, respectively. Following i.v. dosing of YO, the mean apparent terminal half-life of 11-OH-YO (347±63 min) was almost four times higher than that of YO (91.0±33.6 min) suggesting an elimination rate-limited kinetics for 11-OH-YO.

Keywords: Yohimbine; 10-Hydroxy-yohimbine; 11-Hydroxy-yohimbine; Oral bioavailability; Pharmacokinetics; Healthy subjects

1. Introduction

Yohimbine (YO) is a selective α-2-adrenergic antagonist used as a probe for differentiating α-receptor subtypes (Goldberg and Robertson, 1983). YO can also be used as a probe to evaluate the sympathetic reactivity in essential hypertension (Goldstein et al., 1991) and vulnerability to affective and anxiety disorders (Mendlewicz et al., 1989). YO is also used as a pharmacologic probe of the central noradrenergic system. Indeed, it has been shown, following YO administration, that the increase in cerebrospinal fluid levels of norepinephrine in normal older persons and patients with Alzheimer's disease was higher than those measured in young healthy subjects (Peskind et al., 1995).

Yohimbine is used clinically for the management of impotence (Morales et al., 1987), for the treatment of orthostatic hypotension secondary to autonomic failure (Onrot et al., 1987) and tricyclic antidepressant therapy (Lacomblez et al., 1989), dry mouth (Chatelut et al., 1989; Bagheri et al., 1992; Bagheri et al., 1994) and to induce lipid mobilization in obese subjects (Berlan et al., 1991).

The pharmacokinetics of YO has been investigated in young healthy subjects (Owen et al., 1987; Guthrie et al., 1990; Hedner et al., 1992; Sturgill et al., 1997), in normal older persons and patients with Alzheimer's disease (Le Corre et al., 1997) and in middle-aged patients treated with antidepressant drugs (Bagheri et al., 1994) showing that YO has a high and variable plasma clearance. The oral bioavailability of YO was shown to be low and variable (Guthrie et al., 1990). In addition, we have shown that YO was metabolized in at least two metabolites, namely 10-hydroxy-yohimbine and 11-hydroxy-yohimbine (11-OH-YO) (Le Verge et al., 1992), and that both YO and 11-OH-YO are distributed in cerebrospinal fluid (Le Corre et al., 1997). The 11-hydroxy metabolite which is the only metabolite detected in plasma was shown to have α-2-adrenergic antagonist properties (Berlan et al., 1993).

In order to get further insight in the biopharmaceutics and metabolism of YO, we investigated the disposition of yohimbine and of its hydroxylated metabolites following intravenous and oral dosing in healthy subjects.

2. Experimental procedures

2.1. Subjects

The study was performed in 12 healthy male caucasian

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volunteers (22.6±3.7 years and 66.7±7.4 kg) who gave informed consent, at Therapharm Recherches (Boulogne-Billancourt, France). Data for subject 8 were not recovered following oral dosing. All subjects had normal hepatic and renal functions, and were free of all medication for at least 1 month prior to the study.

2.2. Study design

The study was performed following i.v. bolus and oral dosing with a 1-week wash-out period. Subjects fasted overnight and received first a single i.v. bolus of 5 mg (1 ml) of YO and then a single oral dose of 8 mg of YO (four tablets dosed at 2 mg with 200 ml of water, Yohimbine®, Houdé, Paris La Défense, France). Following i.v. dosing, blood was collected just prior to administration and at 2, 5, 10, 15, 30, 45, 60, 90, 120, 180, 240 and 480 min following administration. Following oral dosing, blood was collected just prior to administration and at 15, 30, 45, 60, 120, 240, 360, 480, 720 and 1440 min following administration. Urine was recovered from 0 to 8 h and from 8 to 24 h post-dosing following i.v. administration, and from 0 to 12 h and from 12 to 24 h post-dosing following oral administration.

2.3. Analytical methods

YO and 11-OH-YO in plasma and urine were assayed using a normal-phase high pressure liquid chromatography method with fluorimetric detection (Le Verge et al., 1992). The limits of determination for YO, 10-OH-YO and 11-OH-YO were 0.1, 0.5 and 1.0 ng/ml, respectively. The between-day reproducibilities checked at a concentration of 100 ng/ml were 3.8, 1.4 and 5.9%, respectively.

2.4. Pharmacokinetic analysis

A model with one-exponential or two-exponential functions and first-order elimination from the central compartment was fitted to the YO plasma concentrations obtained after i.v. dosing, using weighted nonlinear least-squares regression analysis with the reciprocal of squared concentration as a weighting factor (WinNonlin version 1.5, Scientific Consulting Inc., Apex, NC, USA). In all but one case, the biexponential function provided a better fit as judged by the distribution of residuals and by statistical comparison of the sum of squared deviations (Boxenbaum et al., 1974). Standard methods (Gibaldi and Perrier, 1982) were used to calculate the following parameters following i.v. dosing: the time-averaged total body clearance (CL), renal clearance (CL_r), apparent volume of distribution of the central compartment (V_c), apparent volume of distribution at steady-state (V_{ss}), distribution rate constants (K_{12} and K_{21}), elimination rate constant (K_{10}), apparent distribution and elimination half-lives ($t_{1/2\alpha}$ and $t_{1/2\beta}$). Non-renal clearance of YO (CL_{nr}) was calculated as follows: $CL_{nr} = CL - CL_r$. The area under the plasma curve from zero to the last sampling point ($AUC_{t\text{-last-iv}}$) and from zero to infinity ($AUC_{\text{-inf-iv}}$) were calculated by linear trapezoidal method from experimental data. The extrapolated area was calculated by dividing the last measured plasma concentration (C_{last}) by the slope of the terminal phase.

After oral dosing, individual YO concentration data were analyzed using non-compartmental analysis assuming a first-order elimination from the central compartment with the software package WinNonlin. Peak plasma concentration (C_{max}) and corresponding time to peak concentration (T_{max}) after oral dosing were derived from raw data. The area under the plasma curve from zero to infinity ($AUC_{\text{-inf-po}}$) were calculated as described above. Standard methods (Gibaldi and Perrier, 1982) were used to determine the following parameters: total body clearance (CL/F), renal clearance (CL_r/F), apparent volume of distribution at pseudo-distribution equilibrium (V_z/F), and apparent elimination half-lives ($t_{1/2\lambda z}$). The absolute bioavailability (F) was calculated from the ratio of $AUC_{\text{-inf-po}}$ and $AUC_{\text{-inf-iv}}$.

Individual absorption kinetics after oral administration were evaluated by Loo–Riegelman absorption analysis (Gibaldi and Perrier, 1982; Loo and Riegelman, 1968) using the software SIPHAR (Simed, Créteil, France). The in vivo mean absorption times were determined from the percent absorbed–time plots fitted using the Weibull equation.

The terminal apparent elimination half-life of 11-OH-YO after i.v. and oral dosing of YO was estimated following non-compartmental analysis. The extrapolated area was calculated as described above.

The urinary elimination of YO, 10-OH-YO and 11-OH-YO were expressed as percent of the administered dose. The urinary elimination rates of 10-OH-YO and 11-OH-YO were calculated from the excretion rates and the mid-point times by fitting the pooled data according to a monoexponential function.

2.5. Statistical analysis

A value of $p<0.05$ defined statistical significance. All data are presented as mean±standard deviation (S.D.).

3. Results

The mean plasma concentration–time curves of YO and 11-OH-YO following i.v. ($n=11$) and oral ($n=10$) dosing, and the corresponding plasma concentration–time curve obtained in the slow metabolizer subject, are shown in Figs. 1 and 2, respectively. 10-OH-YO was not detected in plasma but only in urine. The pharmacokinetic parameters of YO following i.v. and oral dosing are listed in Tables 1 and 2, respectively.

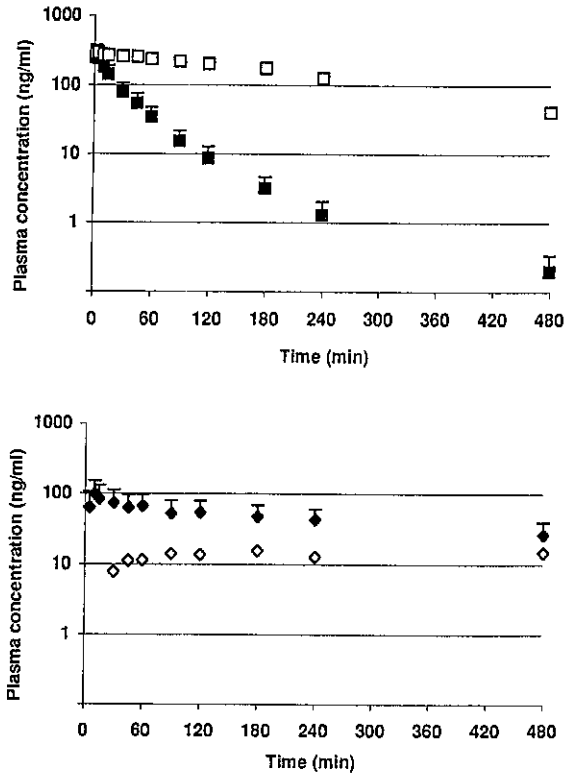

Fig. 1. Top: Mean (±S.D., $n=11$) plasma concentrations of yohimbine (■) and plasma concentrations of yohimbine in a slow-metabolizer subject (□) following i.v. administration of yohimbine at a dose of 5 mg. Bottom: Mean (±S.D., $n=11$) plasma concentrations of 11-hydroxy-yohimbine (✇) and plasma concentrations of 11-hydroxy-yohimbine in a slow-metabolizer subject (◇) following i.v. administration of yohimbine at a dose of 5 mg.

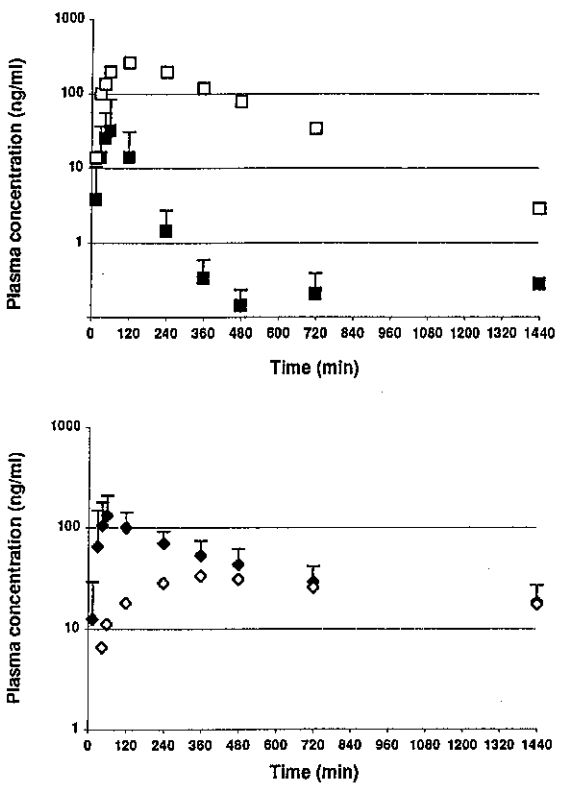

Fig. 2. Top: Mean (±S.D., $n=10$) plasma concentrations of yohimbine (■) and plasma concentrations of yohimbine in a slow-metabolizer subject (□) following oral administration of yohimbine at a dose of 8 mg. Bottom: Mean (±S.D., $n=10$) plasma concentrations of 11-hydroxy-yohimbine (✇) and plasma concentrations of 11-hydroxy-yohimbine in a slow-metabolizer subject (◇) following oral administration of yohimbine at a dose of 8 mg.

Table 1
Pharmacokinetic parameters of yohimbine following i.v. administration at a dose of 5 mg in 12 subjects

Subjects	AUC_{∞} (ng/min/ml)		CL (l/min)	CL_r (l/min)	V (l)	V_{ss} (l)	K_{12} (min)	K_{21} (min)	K_{10} (min)	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)
	YO	11-OH-YO									
S1	8766	47 337	0.594	0.002	24.4	35.4	2.3	5.0	24.3	25.6	154.7
S2	3962	23 869	1.335	0.009	42.3	63.5	5.9	11.8	31.5	17.4	74.3
S3	10 126	20 869	0.667	0.002	26.5	32.8	1.7	7.2	25.2	25.2	105.8
S4	7246	27 848	0.721	0.002	25.0	32.2	2.5	8.7	28.8	21.5	89.1
S5	9072	71 518	0.571	0.001	19.5	25.1	3.0	10.4	29.3	20.6	76.3
S6	11 080	28 948	0.485	0.003	14.5	20.4	7.1	17.3	33.5	15.4	53.8
S7	7085	47 037	0.754	0.003	21.4	26.3	2.0	8.9	35.2	18.3	84.2
S8	7387	41 942	0.723	0.005	20.5	28.0	1.8	4.8	35.3	18.6	152.5
S9[a]	77 777	–	0.057	0.001	17.4	–	–	–	–	–	210.0
S10	13 828	36 991	0.387	0.003	13.1	18.0	4.5	11.9	29.6	19.1	71.3
S11	6548	19 137	0.795	0.002	30.0	35.9	2.3	11.7	26.5	22.9	67.5
S12	5426	16 563	0.976	0.002	28.4	36.1	2.9	10.9	34.3	18.1	71.2
Mean	8230	34 733	0.728	0.003	24.1	32.2	3.3	9.9	30.3	20.2	91.0
S.D.	2756	16 386	0.256	0.002	8.0	12.1	1.8	3.6	4.0	3.3	33.6

[a] Data from S9 are not used in calculation of mean and S.D.

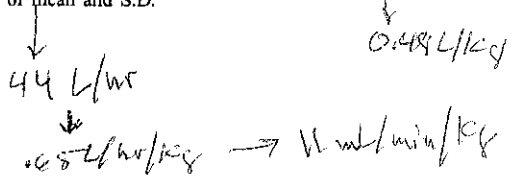

Table 2
Biopharmaceutic and pharmacokinetic parameters of yohimbine following oral administration at a dose of 8 mg in 11 subjects.

Subjects	AUC_{-inf} (ng/min/ml)		C_{max} (ng/ml)	T_{max} (min)	F (%)	V_z (l)	CL_r (l/min)	$t_{1/2\lambda z}$ (min)	t_d (min)
	YO	11-OH-YO							
S1	3683	119 762	30.7	45	26.3	52	0.002	64	115
S2	881	49 644	4.5	45	13.9	153	0.004	84	168
S3	1010	38 827	5.0	120	6.2	186	0.001	261	389
S4	500	59 001	3.4	120	4.3	37	0.001	37	144
S5	1991	94 983	18.8	120	13.7	19	0.001	24	166
S6	13 768	98 271	171.0	60	77.7	27	0.003	41	117
S7	629	63 911	5.9	60	5.5	127	0.002	125	128
S8	–	–	–	–	–	–	–	–	–
S9[a]	105 596	63 799	266.1	120	84.9	19	0.001	200	61
S10	6543	151 783	73.1	30	29.6	27	0.002	52	99
S11	2678	63 323	30.8	45	25.6	54	0.003	49	110
S12	1759	79 709	29.9	45	20.3	31	0.001	23	86
Mean	3344	81 921	37.3	69	22.3	71	0.002	76	152
S.D.	4093	34 721	51.5	36	21.5	61	0.001	72	87

[a] Data from S9 are not used in calculation of mean and S.D.

The modelling of oral data led to a poor evaluation of pharmacokinetic parameters as estimated by the coefficient of variation of the parameters. Hence, a noncompartmental analysis was performed. Following i.v. and oral dosing, the average extrapolated area of YO concentrations was 1.3 and 2.1%, respectively.

Oral absorption of YO was rather slow as displayed by the T_{max} and absorption times and illustrated by the in vivo absorption kinetics (Fig. 3).

YO bioavailability was highly variable ranging from 4.3 to 84.9%. Two subjects (S6 and S9) displayed a high bioavailability: 77.7 and 84.9%, respectively. However, S9 should be considered apart because he was shown to be a poor metabolizer. Indeed, following i.v. and oral dosing, its AUC_{-inf} was respectively around ten and 30 times higher than the mean AUC_{-inf} of the rest of the group. S6 had a pharmacokinetic pattern comparable to that of the rest of the group following i.v. dosing, with AUC_{-inf} for 11-OH-YO and YO which were close to the mean AUC_{-inf} of the group. However, following oral dosing the ratio of AUC_{-inf} between 11-OH-YO and YO was around 7 while it was 24 for the rest of the group. Hence, a lower enterocyte metabolism may have occurred in this subject.

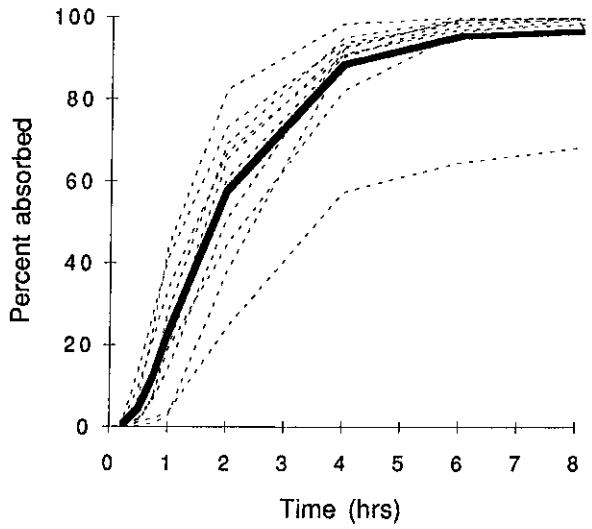

Fig. 3. Individual percent absorbed–time plots ($n=10$, dotted lines) and mean absorption profile (full line) of yohimbine following oral administration at a dose of 8 mg.

Following i.v. dosing of YO, 11-OH-YO displayed biexponential and monoexponential declines in seven and four subjects, respectively. The mean apparent terminal half-life of 11-OH-YO (347±63 min) was almost four times higher than that of YO, without difference between biexponential pattern (355±49 min) and monoexponential pattern (348±75 min). Following oral dosing, 11-OH-YO displayed a biexponential decline in all subjects with a mean apparent terminal half-life of 855±212 min. Following i.v. and oral dosing, the average extrapolated area of 11-OH-YO concentrations was 35 and 27%, respectively.

Following i.v. dosing, the accumulated renal excretion of YO, 10-OH-YO and 11-OH-YO were 0.007±0.007, 0.015±0.006 and 0.692±0.125 mg, respectively. The overall excretion of YO, 10-OH-YO and 11-OH-YO represented 0.15±0.14, 0.29±0.12 and 13.8±2.5% of the dose of YO administered, respectively. Following oral dosing, the accumulated renal excretion of YO, 10-OH-YO and 11-OH-YO were respectively 0.004±0.005, 0.022±0.009 and 1.146±0.187 mg, corresponding to 0.05±0.06, 0.3±0.1 and 14.3±2.3% of the dose administered.

The average elimination half-life of 11-OH-YO, determined from the urinary excretion rates, was 519±136 and 514±66 min following i.v. and oral dosing, respectively. The average elimination half-life of 10-OH-YO, determined from the urinary excretion rates, was slightly lower than that of 11-OH-YO: 403±137 and 380±104 min following i.v. and oral dosing, respectively. The elimina-

tion half-life of YO could not be determined from urinary data because YO was not detected in the second urine samples confirming its higher elimination rate observed from plasma data in comparison to 11-OH-YO.

4. Discussion

The mean plasma *CL* of YO (11.0±3.8 ml/min/kg) was very close to that reported by Guthrie et al. (1990) in healthy subjects (9.8±4.5 ml/min/kg), approaching liver plasma flow (11.6 ml/min/kg) (Davies and Morris, 1993). These data contrast with those reported by Hedner et al. (1992) who found a mean plasma clearance around 2 l/min leading them to hypothesize an extra-hepatic metabolism. In the slow metabolizer subject, in whom the biotransformation of YO to 11-OH-YO cosegregated with the debrisoquine oxidative polymorphism (R. Le Verge, pers. commun. 1994), *CL* was 15 times lower than in the rest of the group. The magnitude of CL_{nr} of Y0 suggested a significant metabolism and/or extra-renal excretion.

Hedner et al. (1992) found a relatively large volume of distribution for YO suggesting an extensive tissue distribution (V_{ss} ranging 37–127 l). In the current study, the distribution pattern of YO was different (Table 1) with a twice lower and much less variable V_{ss}. Given to its high lipid solubility, YO would be expected to have a significant tissue distribution even though it has a rather high (around 80%) protein binding in humans (Berlan et al., 1993). However, the value of V_{ss} was lower than total body water volume. Such a relatively low distribution could be explained by the relative magnitude of elimination rate constant and distribution rate constants. Indeed, the fate of drug molecules in the central compartment is elimination and transfer to the peripheral compartment, the rate constants for these processes indicating the probability of their occurrence (Abramson, 1981). Hence, from a probabilistic point of view, given the ratio between K_{10} and K_{12} (around 9), YO has a 90% chance of being eliminated and a 10% chance of being transferred to the peripheral compartment. Moreover, given that K_{21} was three times higher than K_{12}, a rapid redistribution from tissues probably occurs. Hence, a rather low tissue distribution was likely for YO.

The mean apparent elimination half-life (91.0±33.6 min) was close to that observed following oral administration (88.4±14.1 min) and was less variable and almost twice higher than those reported previously following i.v. dosing of YO: 41±13 min (Guthrie et al., 1990) and 38±36 (Hedner et al., 1992). Such a difference also appeared in the values of the distribution half-life which was much smaller and highly variable in those reports. The mean distribution half-life was 5.6±7.0 min (Guthrie et al., 1990) and 3.5±5.2 (Hedner et al., 1992). In the latter report, $t_{1/2\alpha}$ ranged from 0.3 to 18.4 min and was strangely low ($t_{1/2\alpha}$<1.1 min) in seven subjects. The difference in apparent distribution and elimination half-lives between studies may result from fitting procedure (e.g. weighting scheme). We had to use a $1/y2$ weighting factor to obtain a suitable fit of the plasma concentrations allowing to take into account the last data points of the terminal elimination phase (the time course of i.v. YO displayed a 3 log scale variation in most of the subjects).

YO displayed a rather slow absorption that may be related to its high lipophilicity. A higher absorption rate of YO was described by Guthrie et al. (1990) with a T_{max} occurring within 10–45 min following administration. Such a difference in absorption rate is not unlikely given that YO was given as a solution in Guthrie's work. Indeed, it can be hypothetized that YO belongs to the class II of the biopharmaceutic drug classification (i.e. low solubility and high permeability) given to its high lipophilicity and to its distribution pattern which suggests a rapid tissue distribution. Such drugs are expected to have a variable absorption due to formulation variables as well as to in vivo variables (Amidon et al., 1995).

YO bioavailability was highly variable and close to the data previously reported (mean±S.D., 33±26%) (Guthrie et al., 1990).

In the assessment of bioavailability of YO, and more importantly in the assessment of bioequivalence of YO products, the 11-OH-YO metabolite may be considered. Indeed, the following reasons should be considered: (i) the average *AUC* of 11-OH-YO are about four and 25 times higher than those of YO following i.v. and oral dosing, respectively, (ii) the plasma concentrations of 11-OH-YO are much less variable than those of YO following oral dosing (42 vs. 122%), (iii) 11-OH-YO has been shown to have α-2-adrenergic antagonist properties on ex vivo models, (iv) 11-OH-YO has a much longer apparent elimination half-life.

Compared to i.v. dosing, the slowest apparent terminal half-life of 11-OH-YO observed following oral dosing may be apparent and result from the fact that plasma levels were not measured above 480 min following i.v. dosing while plasma levels were measured until 1440 min following oral dosing. Indeed, Pang and Gillette (1980) indicated that the terminal slope of the metabolite curve after about four half-lives of the parent drug can be used to estimate the elimination rate constant of the metabolite in the case where the overall elimination rate constant of the parent drug is higher than that of the metabolite.

The rate limitation in metabolite kinetics is controlled by the inter-relationship between clearance and volume of both drug and metabolite (Houston and Taylor, 1984).

The slowest apparent elimination of 11-OH-YO, compared to YO, suggests that the metabolite has an elimination rate-limited kinetics, i.e. a terminal slope governed by its own half-life. Such a slowest apparent elimination of 11-OH-YO was also observed in a previous study (Le Corre et al., 1997).

The pooled renal excretion of parent drug and hydroxylated metabolites reached about 15% of the dose adminis-

tered whatever the route of administration. This urinary excretion balance suggests that YO (and/or its hydroxylated metabolites) should be: (i) excreted by a non-renal pathway (biliary excretion), (ii) biotransformed in unknown metabolites. However, a significant biliary excretion should be unlikely given that no sign of entero-hepatic was evidenced.

The higher excretion of 11-OH-YO compared to YO may be related to its lower lipophilicity and to its twice lower plasma protein binding (around 40 and 80% for 11-OH-YO and YO, respectively) (Berlan et al., 1993). The mean renal clearance of YO following i.v. and oral dosing represented on average 0.15 and 0.04% of the total plasma clearance, respectively. A higher implication of renal clearance in overall elimination of YO was reported by Hedner et al. (1992) (mean 3.4%). In the slow metabolizer subject, the renal clearance was 1.0 and 1.4% of total i.v. and oral plasma clearance, respectively.

5. Conclusion

The current investigation is the first report describing the i.v. and oral pharmacokinetics of YO and of its metabolites (i.e. 10-OH-YO and 11-OH-YO). The oral bioavailability of YO was low and highly variable and its oral absorption was rather slow when administered as a marketed solid dosage form. The total plasma clearance of YO was high, excepted in one subject who was a slow-metabolizer. Contrary to previous reports, YO displayed a rather low distribution. 11-OH-YO was present in plasma and urine and had elimination rate-limited kinetics. 10-OH-YO was only detected in urine. The urinary excretion balance indicated that YO had a negligible renal clearance and suggested that YO (and/or its hydroxylated metabolites) should be excreted by a non-renal pathway (biliary excretion) and/or biotransformed in unknown metabolites.

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